UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/961,443	10/30/97	TOWNES T	04005/013003

023859
NEEDLE & ROSENBERG P C
127 PEACHTREE STREET N E
ATLANTA GA 30303-1811

HM12/1010

EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	22

DATE MAILED: 10/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/961,443	Applicant(s) TOWNES ET AL.	
	Examiner Deborah Crouch	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) 20 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19,21-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election without traverse of group I, claims 1-19 and 21-24 in Paper No. 8 is acknowledged.

Claims 1-24 are pending. However, claim 20 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention. Election was made without traverse in a paper no. 8. Claims 1-19 and 21-24 are under current examination.

Applicant is advised that the examiner assigned this application has changed. The new examiner is Deborah Crouch, Ph.D., AU 1632, whose telephone information can be found in the signature paragraph at the end of this office actions.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the post office address of each inventor. A post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The post office address should include the ZIP Code designation.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-14, 19, 21 ,23, and 24 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-15 and 17-19 of copending Application No. 08/934,385. This is a double patenting rejection.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15-18 and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 and 17-19 of copending Application No. 08/934,385. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant claims and the '385 claims contain subject matter directed to a transgenic nonhuman mammal comprising erythrocytes that produce a human hemoglobin, but fail to product adult hemoglobin endogenous to said nonhuman mammal. However, the instant claims are directed to specific types and combinations of human hemoglobin genes which are encompassed within the claims of the '385 application. Therefore, the instant claims and the '385 claims contain overlapping subject matter which renders the instantly claimed invention obvious absence evidence to the contrary.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 35 USC § § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

Claims 1-19 and 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "transgenic mouse whose genome comprises a human LCR γ-β hemoglobin switching DNA construct, wherein said genome is further homozygous for murine α- and β-globin knockout alleles such that said knockout alleles result in said mouse failing to synthesize murine hemoglobin, and wherein said hemoglobin switching construct is expressed such said mouse develops hemolytic anemia", does not reasonably provide enablement for a transgenic nonhuman mammal comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said nonhuman mammal." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the production of transgenic mice (adult HbS) who develop severe hemolytic anemia as a result of the production of human hemoglobin in the absence of murine hemoglobin, thus, providing a mouse model that closely approximates the fetal to adult globin genes in man. Applicants teach that the construction and use of a DNA switch construct is necessary to delay hemoglobin switching and prevent potential perinatal lethality. See page 25, lines 10-14. Applicants teach "how to use" the HbS mice as models for sickle cell disease because these mice develop significant *in vivo* pathology at a relatively young age under ambient conditions. Furthermore, Applicants teach "how to use"

the transgenic mice of the invention according to its phenotype, the development of hemolytic anemia. Applicants report that "hemolytic anemia develops during the first few weeks of life as the level of HbF declines in these mice," and that "this temporal pattern of onset mimics the onset of anemia in human sickle cell infants during the first few months of life." See page 28, lines 13-19. As such, the specification teaches "how to make" transgenic mice whose genome comprises the essential DNA switch construct as well as knockout mutation in the endogenous α- and β-globin genes such that no murine hemoglobin is produced, such that one of skill would know "how to use" the transgenic mouse which develops the corresponding phenotype, hemolytic anemia.

With regard to the scope of the claimed invention, Applicant's claims are directed to transgenic non-human mammals whose genome comprises knockout mutations in endogenous globin genes. As such, the specification discloses the technology of making transgenic mice utilizing embryonic stem (ES) cells. However, the prior art and post-filing art are replete with references which indicate that ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. (J. Mol. Med., 1997), page 214, Summary. In addition, Seamark (Reproductive Fertility and Development, 1994) discloses that totipotency of ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Mullins et al. (Journal of Clinical Investigation, 1996) disclose that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated" (page S38, col. 1, first. parag.). As the claims require introduction of a knockout construct into an ES cell, the state of the art supports that only mouse ES cells were available for use for production of transgenics.

Furthermore, the claimed invention is directed to transgenic nonhuman mammals whose genome comprises a human globin transgene(s). However, without evidence to the contrary, transgene expression in different species of transgenic nonhuman mammals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically

supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs, however only transgenic mice exhibited an increased growth due to the express of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). The observation is further supported by Mullins et al. (Journal of Clinical Investigation, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall also supports this observation by stating that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. Wall further reports that "transgenic expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from Differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph, bridging pages 238-239). Given such species differences in the expression of a transgene, it would have required undue experimentation to extend the results achieved in transgenic mice to the levels of transgenic product in any other transgenic nonhuman mammal, the consequences of that production, and therefore, the resulting phenotype.

Furthermore, it is emphasized that transgenic elements such as promoter, enhancer, coding and non-coding sequences, presence or absence of introns, ect., are all determining factors in the production of transgenic nonhuman mammals, wherein the transgene is expressed at a level sufficient to convey a correlatable phenotype. e.g., hemolytic anemia. The phenotype renders the animal useful as taught by the

specification , i.e., the specification teaches "how to use" the transgenic animals as models for sickle cell disease. As such, the issue here is that applicants fail to teach or provide a clear correlation for "how to make" a transgenic nonhuman mammal, other than a mouse, using a transgenic comprising human globin genes, wherein the animal expresses the transgene at levels sufficient for 'how to use" it as taught by the specification. Thus, as unpredictable transgene behavior is supported by the cited references of record, the state of the art cannot be relied upon to provide the nexus between the exemplified HbS mice and other transgenic nonhuman mammals.

With regard to the enabled scope of human hemoglobin transgene, applicants provide evidence of the necessity utilizing a DNA "switch construct" for the generation of the transgenic mice of the invention. Applicants report that the precise regulatory sequences that control human γ- to β-globin gene switching are unknown, but suggest that the LCR γ-β transgene contains most if not all of the necessary sequence for correct switching. See page 21, lines 24-27. Applicants fail to teach such a "switching" effect from any other regulatory sequence or region, or even that any other regulatory region would h ave such "switch" function. As such, the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. *Ex parte Maizel*, 27 USPQ2d 1662 (BPAI 1992). Therefore, the claims should be specifically limited to comprise at least those necessary elements of the disclosed DNA switch construct, the LCR γ-β transgenic, as applicants appear to provide evidence that their results are unexpected.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of transgenic nonhuman mammals of more than one species expressing a human γ-β globin "switch" transgene as well as comprising endogenous knock out mutations of the α- and β-globin genes, in particular, in view of the underdeveloped state of the ES cell art for species of mammals other than mice, the unpredictable state of the art with respect to the generation of transgenic non-human mammals of al species expressing identical

levels of a transgene and developing identical phenotypes due to such expression, and the breadth of the claims, it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed with a reasonable expectation of success.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paszty et al (Ref. Q or paper no. 5) and Ciavatta et al (Ref. G of paper no. 5) taken with Rubin et al (Journal of Clinical Investigation, 1991) and Fabry et al (Ref. I of paper no. 5).

The claimed invention is directed to transgenic nonhuman mammals comprising erythrocytes that produce a human hemoglobin, but fail to product adult hemoglobin endogenous to said nonhuman mammal.

Paszty et al . teach the generation of knock out mice mutant for both adult α-globin genes. Paszty et al. teach rescue of the lethal phenotypes by introduction a human α-globin gene. Ciavatta eta l teach targeted deletion of mouse β^{maj}- and β^{min}- globin genes in mouse embryonic stem cells. Ciavatta et al. further suggests appropriate matings between α-thalassemic mice and mice that synthesize high levels of human sickle cell hemoglobin (HbS) for the production of mice that synthesize HbS exclusively. See page 9262, col. 1. As such, at the time of the instant invention both Rubin et al. and Fabry et al. teach the production of transgenic mice expressing HbS and/or HbS-Antilles transgenes.

According, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to mate the α-globin mutant mice of Paszty et al. with the β-globin mutant mice of Ciavatta et al. to produce transgenic mice comprising knockouts in the endogenous globin genes which knocking in the human globin genes for rescue of the lethal phenotypes, or by mating the mice mutant for

the endogenous globin genes with a transgenic mouse expressing high levels of HbS with a reasonable expectation of producing a transgenic mouse production human hemoglobin in the absence of the production of endogenous hemoglobin.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of results to the contrary.

Claims 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paszty et al and Ciavatta et al taken with Rubin et al and Fabry et al, as applied to claims 1-91 above, and further in view of Westphal (FASEB J, 1989).

The combination of Paszty et al and Ciavatta et al taken with Rubin et al and Fabry et al do not specifically suggest using the mouse models for screening methods, although they suggest creating better models for sickle cell disease (see pages 9262, col. 2 of Ciavatta et al.). However, at the time the claimed invention was made, Westphal et al. teach that the potential use of homologous gene targeting for biotechnology becomes obvious if we think about the genes that are affected in human genetic disorders. Specifically, Westphal discuss that mice carrying specific globin gene defects would be invaluable in designing remedies and screening drugs for the most frequent of all serious human disorders, thalassemia and sickle cell anemia. See page 120, column 1, 3rd paragraph.

Accordingly, in view of the teachings of Westphal, it would have been obvious for one of ordinary skill in the art to utilize the transgenic mouse models of the combination of Paszty et la., Ciavatta et al., Rubin et al., and Fabry et al. for designing remedies and screening drugs with a reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of results to the contrary.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even

though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126. The examiner's SPE is Karen Hauda, whose telephone number is (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Art Unit Patent Analyst, Zeta Jones, whose telephone number is (703) 305-3291.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630

Dr. D. Crouch
October 9, 2001